

Development of drug regulating authorities

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Primitive man thought that disease was of supernatural origin, a thunderbolt from the gods who therefore had to be placated before relief could be obtained. As man took over these god-like roles the community grudgingly accepted his skills but imposed legal constraints on his arrogated powers. Today the Code of Hammurabi is preserved in the Louvre, engraved on a pillar of hard stone. This is the earliest legal code protecting patients from inadequate treatment named after King Hammurabi of Mesopotamia several thousand years ago. Physicians neglecting their patients or providing a wrongful treatment were severely punished and in serious cases the penalty could be mutilation.

From earliest times there grew up an awareness that some herbs were toxic. Homer in his *Odyssey* noted the healing nature of some drugs and others which could be harmful. Egyptian medicine and therapeutics dominated the ancient world for two thousand years but there were rigid controls of the system laid down in the sacred book. If a patient died and the practitioner had deviated in any major fashion from the basic tenets then he was submitted to a trial with death as the possible penalty. In Hippocratic medicine drug therapy did not play a major part but there were some legal constraints as is evidenced by an inscription dated from 4th century BC found on the Acropolis at Athens. This commemorated that Evanor, the Physician, had been chosen inspector of drugs. The sophisticated Roman civilisation was correctly sceptical of medicine and any form of treatment and of doctors and developed techniques for detecting the adulteration of drugs as recorded in the *Materia Medica* of Dioscorides. In mediaeval Moslem countries the office of the *Hisba* in the early part of the 9th century enforced religious codes of public morality but in addition sent out officials who were given specific instructions to inspect the syrups and drugs of their shops any time of the day or night. These inspectors, trained as apothecaries, reported on infringements of rules which could lead to punishment including heavy fines, the bastinado and the pillory.

The control of the quality of medicines and their standards probably first began in Europe in

the School of Salerno in the 13th century and then moved to the low countries, Germany, France and to England and Scotland in the 15th and 16th centuries. As early as 1423 the city authorities of London appointed drug inspectors. In 1540 Henry VIII empowered the Royal College of Physicians of London to appoint four fellows of the College as inspectors of apothecaries' wares in the London area. The London Pharmacopoeia of 1618 became applicable to all England and eventually this was replaced by the uniformity and influence of the British Pharmacopoeia of 1864. Here in Scotland the Charter for the Faculty of Physicians of Glasgow in 1599 granted by James VI of Scotland gave power to inspect and control the drugs sold in Glasgow, a power which rested for many years in the hands of the Visitor. In Edinburgh the Edinburgh Pharmacopoeia was published in the late 17th century and its early editions were used by the physicians to assert their authority to control drugs in Edinburgh and to attempt to limit the growing power of the apothecaries.

The advance of therapeutics was little influenced by the scientific progress of the 17th and 18th century. For example, Robert Boyle the great chemist, wrote in 1661 'The Sceptical Chemist' and provided foundations for modern chemistry. Yet the same man when dealing with human therapeutics wrote in 1692 'A collection of choice remedies', describing a hotchpotch of messes with ingredients such as worms and horse dung and human urine and moss from a dead man's skull. None the less, the basis of rational therapeutics was laid down in the 18th century, through for example the clinical trial carried out by James Lind (1747) in HMS Salisbury in the English Channel on six pairs of sailors with scurvy. William Withering in 1775-85 not only introduced digitalis for dropsy but defined its main indication in cardiac dropsy and fought for its retention despite the adverse effects due to its narrow therapeutic range. Modern therapeutics was beginning with such foundations of critical analysis and observation of action of drugs.

There followed a long gestation period before these first beginnings developed into a generalised system of rational medicinal care. In the

interim period up to the end of the 19th century, and the beginning of this century, the revolution which was taking place in scientific understanding and particularly in the working of the human body was not matched by any startling advance in the range of medicinal treatments. It was as if the changes in the wider scientific world had paralysed the physician into a form of therapeutic nihilism. It was only in this century that this torpor was ended by the drama of the introduction of insulin, then liver therapy and antibiotics. Once the spell was broken, the development of new medicines has followed rapidly up to the present day—a veritable drug explosion in which every practising doctor takes part in his daily care of patients.

It was only when these advances in therapeutic science had taken place that a meaningful system of drug regulation as we know it could arise. The Gin Acts of the 18th Century and the Sale of Food and Drug Acts of 1875 in the Disraeli administration were the only general statutes in this field until 1925 when the Therapeutic Substances Act was passed controlling medicinal products of biological origin such as vaccines, sera, blood products, insulin and cat-gut sutures. A few other statutes had however been passed to deal with particular problems—the Venereal Diseases Act of 1917; the Cancer Act of 1939 and the Dangerous Drugs Act of 1930, the latter being amended up to 1965 and eventually succeeded in the 1970s by the Misuse of Drugs Act. Each recognised certain dangers to the community, for example, drug addiction and irresponsible advertising of drugs for serious disorders.

It was of course the thalidomide tragedy which provoked the activity leading to the co-ordination of legislation of safety of medicines. The Dunlop Committee showed the way in which government, industry and the medical profession who have so much to contribute together could harmonise their efforts even in a voluntary fashion. Statutory control was necessary because all sides of the House of Commons thought that the voluntary arrangements were not sufficient. Thus there followed the Medicines Act of 1968 which came into force in 1971 and provided the powers to control pharmaceutical manufactures and introduced the requirements to assess efficacy in addition to safety and quality—a very important addition to the functions of the Committee on Safety of Drugs. Section 4 of the Act empowered the Government to create several expert advisory committees and these are currently the Committee on Safety of Medicines (CSM), the Committee on the Review of Medicines, the Committee on Dental and

Surgical Materials and the Veterinary Products Committee. The Medicines Commission, set up under Section 3 of the Act, has the function of giving advice to ministers on general matters relating to the Act and of acting as an appellate body from the Committees. It also supervises the work of the British Pharmacopoeia Commission which is responsible for producing the British Pharmacopoeia.

The CSM is not an executive body but an advisory committee to the Licensing Authority with whom powers of licensing and enforcement rest. There are three main subcommittees which consider specialised aspects of medicines under the aegis of the Committee on Safety of Medicines, namely the Chemistry and Pharmacy Subcommittee, the Biologicals Subcommittee and the Safety, Efficacy and Adverse Reaction Subcommittee.

The functions of the CSM under the Medicines Act covers three broad areas: (i) consideration at the request of the Licensing Authority of the safety, quality and efficacy of drugs before use in a clinical trial, leading to advice on the issue of a clinical trial certificate, valid for two years; (ii) similar consultation leading to advice on the grant of a product licence, valid for 5 years and renewable, allowing the product to be marketed; and (iii) surveillance of each drug after marketing so that adverse reactions can be monitored and documented. I cannot here go into detail on this most important subject, namely adverse reactions, except to say that in the United Kingdom it is an aspect of drug regulation to which we are giving the closest attention.

In Europe, as in the United Kingdom, the post-war period was associated with an expanding drug industry and there was a general increase of legislation for drug safety. A new departure occurred in 1957, with the Treaty of Rome, and the formation of the EEC. There were no specific regulations for drugs in that Treaty but there was an emphasis on the free circulation of goods as well as a recognition that national action might be needed in the interests of safety. Since 1965 there have been EEC Directives to bring greater approximation between the various drug licensing systems and in 1975 the Committee for Proprietary Medicinal Products, the CPMP, was created under Directive 75/319/EEC. This committee provides a vehicle for considering marketing authorisations on a community wide basis but its opinions are not binding. The CPMP is composed of representatives from all member states and from the EEC Commission. It also discusses problems of common interest particularly on exchange of information relating to adverse drug reactions.

Its role in marketing authorisations is invoked when a company has obtained a marketing authorisation in one member state and wishes to obtain similar authorisations in five or more member states (two or more states from November 1985 onwards). After submission to the CPMP and to the member states in question the various states concerned have 120 days in which to raise objections. If objections are raised during this time the CPM must meet within 60 days to discuss the application and give its opinion. This opinion is transmitted to each member state concerned which then has 30 days in which to determine the action they should take. There are obvious differences in the standards of assessment of products between member countries, but the discussion in the CPMP tends to concentrate on the most demanding of these, a fact which should eventually raise the general standards of safety, quality and efficacy of medicinal products.

The European Free Trade Association (EFTA) includes Austria, Finland, Norway, Sweden and Switzerland. Since 1965 moves for the mutual recognition of scientific data have taken place and in 1979 there was enacted 'The scheme for the mutual recognition of evaluation reports on pharmaceutical products'. Up to 1982 14 requests have been put forward although none has been successful.

Among the other countries of Europe the Council of Mutual Economic Assistance (CMEA) includes the USSR, Bulgaria, Czechoslovakia, the German Democratic Republic, Hungary, Poland and Rumania. There is an association with three other countries to the CMEA namely Cuba, Mongolia and Yugoslavia. In these countries drug licences are based on pre-clinical and clinical studies which have been carried out by or controlled by specialised units of institutes. There is co-operation on acceptable standards among these countries. Regular conferences are held among their health ministries.

From 1880, for about 25 years the Department of Agriculture in the United States submitted more than 100 bills to Congress for the purpose of regulating food and drugs. None of these bills was approved until the passage of the Food and Drugs Act of 1906 which empowered the Department of Agriculture to regulate adulterated products, meaning medicines or foods containing harmful materials and misbranded products which were defined as medicines or foods that claim to contain active ingredients but in fact did not. There was no requirement of any safety or efficacy testing by the manufacturer. In 1943 following many deaths from the use of elixir of sulphonamide containing a toxic solvent

(diethyleneglycol) the original act was repealed and the Federal Food, Drug and Cosmetic Act was approved. It established requirements for registration by the manufacturer, testing for safety and factory inspection. In 1951 the Durham-Humphrey Amendment to the Food, Drug and Cosmetic Act established requirements for the regulation of prescription drugs. In 1962, after the thalidomide tragedy the Kefauver-Harris Amendment was approved by Congress and this established the requirement for the pre-market submission of both safety and efficacy data to the food and drugs administration. These data included the investigational new drug application (IND) and the new drug application (NDA). In 1966 the FDA began an extensive review of over-the-counter drug products. The Food and Drug Administration (FDA) has been assigned the executive authority to monitor inter-state commerce of all food, drugs, medical devices and cosmetic products. Within the FDA there are a number of operating units which appoint advisory committees and technical consultants to assist in the review of data and product applications submitted to the Agency.

Thus, in many countries throughout the world there has been the development of drug regulatory authorities. The standards of these authorities have wide variations. There are movements to develop systems of harmonisation of applications for product licences between various groupings, for example in the EEC. Although there are many problems associated with this process the eventual effect should be to raise standards. An even more immediate need is the communication throughout the world of adverse reactions to drugs. Much has been done in this sphere through the World Health Organisation and other bodies but, as Dr Griffin (1986) has explained in his paper for this meeting, a great deal remains to be done before adverse reaction data from different countries can be looked at across the board.

When one looks at the broad canvas of the history of drug regulation, it is however clear that our generation has responded vigorously to the unique challenge of the modern drug explosion. There is no room for complacency. These challenges will not diminish in the coming years. The price of drug safety is constant vigilance not only by the professions and government, but by an educated and well-informed community.

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